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| EXAMINER | |
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| PENG, BO | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/516,578 | SANDERS ET AL. | |
| | Examiner | Art Unit | |
| | BO PENG | 1648 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *28 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *3,4,7,12 and 14-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,6,8-11 and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/26/07&3/17/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Restriction election*

1. Applicant's election without traverse of Group I, directed to a pseudotyped retrovirus, and species of Mo-MuLV as the retroviral core and control elements, and a protein as biomolecule, in the reply filed on December 28, 2007, is acknowledged. Because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Accordingly, Claims 1-25 are pending. Claims 3, 4, 7, 12 and 14-25 are withdrawn as non-elected. Claims 1, 2, 5, 6, 8-11 and 13 are considered in this Office action.

### *Information Disclosure Statement*

3. The information disclosure statements submitted on November 26, 2007, and March 17, 2008, are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements have been considered by the examiner.

### *Claim Rejections - 35 USC § 112, second paragraph*

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 10 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant

regards as the invention.

6. Claim 10 recites: "... wherein the Ebola glycoprotein contains a deletion of nucleotides 309 to 489 in SEQ ID NO: 1". However, this structural limitation does not meet the following description in the specification Para [0014].

[0014] FIG. 1C shows a portion of the nucleotide sequence (SEQ ID NO: 1) and restriction map of plasmid pEboGP showing the complete coding sequence of Ebola glycoprotein. The coding sequence begins with the ATG start codon at nucleotides 956-958 and ends with the TAG stop codon at nucleotides 2984-2986. The *O*-glycosylation region represented by wild-type codons 309-489, which is deleted in pEboGPΔ309-489, begins at nucleotide 1880 and ends at nucleotide 2422.

7. According the Para [0014], SEQ ID NO: 1 is a sequence of pEboGP. The "nucleotides 309 to 489 in SEQ ID NO: 1" required by Claim 10 does not appear to be the coding sequence of Ebola glycoprotein. Appropriate correction is required.

### *Claim Rejections - 35 USC § 112, first paragraph*

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1, 8 and 13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

10. In making a determination as to whether a claimed invention has been adequately described, the courts have identified certain elements that may be considered. Among

those elements are the knowledge in the particular field, the extent and content of the prior art, the maturity of the technology, and predictability of the aspect at issue. See e.g., *Capon v. Eshhar*, 76 U.S.P.Q. 2d 1078, at 1085 (CAFC 2005). For a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

> "A written description of an invention involving a chemical **genus**, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, **where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...**") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

11. Claims 1, 8 and 13 read on a retrovirus pseudotyped with a glycoprotein (GP) comprising a modified *O*-glycosylation region, the pseudotyped retrovirus having a transduction efficiency into a target cell at least 2-fold higher than a retrovirus pseudotyped with the wild-type GP.

12. The scope of the claims encompasses **a subgenus** of retroviruses pseudotyped with modified GPs that have transduction efficiency at least 2-fold higher than those with the wild-type GP in **a genus** of retroviruses pseudotyped with any modified GPs in *O*-glycosylation region. It is noted that either the specification or the claims have provided definition for claim limitation "a glycoprotein comprising a modified O-glycosylation **region**". By definition, "a glycoprotein" is "any of a class of proteins which have carbohydrate groups attached to the polypeptide chain" (see attached citation from Compact Oxford English Dictionary). Moreover, since the specification has not explicitly defined "a modified *O*-glycosylation **region**", "a modified *O*-glycosylation **region**" could be an amino acid sequence in any length that includes a glycosylation site. Thus, "a

modified *O*-glycosylation **region**" could be as small as a few amino acids that include a glycosylation site, or as big as an entire amino acid sequence of GP. As a result, the scope of the claims encompasses **a genus** of retroviruses pseudotyped with any GP that contains any modification.

13. In supporting these claims, the instant specification has disclosed one species: a MuLV retrovirus pseudotyped with Ebola GP containing a deletion of amino acids 309-489 in the *O*-glycosylation region, (Δ309-489GP-psedotyped MuLV). The specification shows that Δ309-489GP-psedotyped MuLV has a transduction level 4.7-fold higher than MuLV pseudotyped with wild type Ebola GP (Examples I and II).

14. The court indicates: "The presence of multiple species within a claimed genus does not necessarily demonstrate possession of the genus. See, In re Smyth, 178 U.S.P.Q. 279 at 284-85 (CCPA 1973) (stating "where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus or combination claimed at a later date in the prosecution of a patent application."); and University of California v. Eli Lilly and Co., 43 USPQ2d 1398, at 1405 (Fed Cir 1997)(citing Smyth for support).

15. In the present case, the art indicates that it is unpredictable in performance of a retrovirus pseudotyped with a glycoprotein comprising a modified *O*-glycosylation region. For example, Brindley evaluated mutant Ebola GPs for their incorporation onto feline immunodeficiency virus (FIV) particles, transduction efficiency, and receptor binding affinity (J. Virology, 81(14):7707-7709, see e.g. Abstract). Brindley showed that FIV virions bearing 39 out of 63 mutant GPs transduced cells efficiently, whereas virions

bearing the other 24 mutant GPs had reduced levels of transduction. Ten mutant GPs were very poorly incorporated onto viral particles. Nine additional mutant GPs competed poorly with wild-type GP for binding to permissive cells. Thus, the art demonstrates that it is uncertain which GPs comprising a modified *O*-glycosylation region can be incorporated into the retroviral core, and which GP mutants have the desired transduction efficiency.

16. Based on the written description requirement, the number of species required to form a representative number varies proportionally with the degree of variability within the claimed genus. In the present case, the specification teaches one species of MLV pseudotyped with a modified Ebola GP (Δ309-489GP-psedotyped MuLV), which has a higher transduction efficiency. However, one species is not sufficiently representative of the claimed subgenus of pesudotyped retroviruses. Given the scope of the claims, and given the high degree of variability that exists in the performance of a retrovirus pseudotyped with a modified glycoprotein, one of ordinary skill in the art cannot envision which retroviruses pseudotyped with a GP comprising a modified *O*-glycosylation region "has transduction efficiency at least 2-fold higher than a retrovirus pseudotyped with the wild-type glycoprotein" encompassed in the scope of the claims. Consequently, the skilled artisan would reasonably conclude that Applicant was not in possession of the pseudotyped retroviruses, which have transduction efficiency at least 2-fold higher than a retrovirus pseudotyped with the wild-type glycoprotein as broadly claimed.

***Claim Rejections - 35 USC § 102***

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

18. Claims 1, 2, 5, 6, 9 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Yang *et al.* (Nature Medcine, 6(8):886-889, cited in IDS), as evidenced by Yang S. (Hum Gene Ther. 1999 Jan 1;10(1):123-32).

19. Claims 1, 2, 5, 6, 9 and 11 are directed to a pseudotyped retrovirus comprising recombinant RNA associated with **a retroviral core** surrounded by a lipid bilayer having disposed therein a glycoprotein comprising a modified *O*-glycosylation region, the recombinant RNA comprising (i) a nucleotide sequence defining a selected biomolecule intended for delivery to a target cell, and (ii) retroviral control elements for packaging, reverse transcription and integration of the retrovirus into a target cell, wherein the retroviral core and control elements are from MuLV and the glycoprotein is a filovirus GP.

20. Yang teaches a pseudotyped murine leukemia virus (MLV, also called as Mo-MuLV) with Ebola virus GP(Δmuc) comprising deletion of a mucin-like domain (*O*-glycosylation region), see e.g. line 2-10, right col. p. 886, and Fig. 1B. Yang's MLV pseudotyped with Ebola GP inherently comprises an MLV core, in view of Yang S (1999) cited as Ref #15 in Yang. Yang S (1999) teaches the DNA constructs encoding MLV core (see Fig. 1), which encodes "recombinant RNA comprising (i) a nucleotide sequence GFP (a selected biomolecule intended for delivery to a target cell), and (ii)

retroviral control elements for packaging, reverse transcription and integration of the retrovirus into a target cell, see e.g. Fig. 1.

21. In view of the teachings, Yang's MLV pseudotyped with Ebola virus GP(Δmuc) meet every structural limitation in the claims, therefore, anticipates Claims 1, 2, 5, 6, 9 and 11.

22. Claims 1, 2, 5, 6, 9 and 11 are rejected under 35 U.S.C. 102(a) as being anticipated by Simmons *et al*. (J. Virology, 76(5):2518-2528, March, 2002, cited in IDS), in view of Wood-Lewis (J. Virology, 72(4): 3155-3160, cited in IDS) and Soneoka Y *et al*. (Nucleic acid Res. 1995, Vol. 23(4):628-633).

23. Simmons teaches a pseudotyped murine leukemia virus (MLV) with Ebola virus GP (filovirus GP) comprising deletion of an *O*-glycosylation region of amino acids 311-463, Fig. 3A. Simmons' pseudotyped MLV with Ebola GP inherently comprises the MLV core, in view of Wood-Lewis (cited as ref #48 in Simmons) and Soneoka (cited as Ref #26 in Soneoka). Wood-Lewis teaches the source of the MLV packaging system; see Para 4, left col. p. 3156. Soneoka teaches the DNA constructs encoding the MLV core (see Fig. 1), which encodes "recombinant RNA comprising (i) a nucleotide sequence lacZ (a selected biomolecule intended for delivery to a target cell), and (ii) retroviral control elements for packaging, reverse transcription and integration of the retrovirus into a target cell, see e.g. Fig. 1.

24. In view of the teachings of Simmons, Wood-Lewis and Soneoka, the MLV pseudotyped with modified Ebola virus GP of the prior art meets every structural

limitation in the claims. Claims 1, 2, 5, 6, 9 and 11 are therefore anticipated by Simmons.

***Claim Rejections - 35 USC § 103***

25. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

26. Claims 8 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Yang or Simmons, as applied in Claims 1, 2, 5, 6, 9 and 11 above, further in view of Wood-Lewis.

This application currently names joint inventors. In considering the patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made, absent any evidence to the contrary. Applicant is advised of their obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

27. Claims 8 and 13 require the pseudotyped retrovirus to have a transduction efficiency into a target cell at least 2-fold higher than a retrovirus pseudotyped with the wild-type GP.

28. The relevance of Yang or Simmons is set forth *supra*. However, neither Yang nor

Simons explicitly teaches that the pseudotyped MLV with a modified Ebola GP has a transduction efficiency into a target cell at least 2-fold higher than a retrovirus pseudotyped with the wild-type GP.

29. However, it was routine practice in a lab to characterize transduction efficiency into target cells, as evidenced by Wood-Lewis. Wood-Lewis teaches characterizing transduction efficiency of MLV pseudotyped with Ebola GP in a variety of target cells, see e.g. bridge paragraph between left col. and right col. p. 3157, and Table 1.

30. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to characterize the transduction efficiency of MLV pseudotyped with modified Ebola GP taught by Yang or Simmons, and identify specific clones of MLV pseudotyped with a modified GP that have higher transduction efficiency that those with wild type GP.

***Remarks***

31. No claim is allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bo Peng, Ph.D. whose telephone number is 571-272-5542. The examiner can normally be reached on M-F, 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/BO PENG/
Examiner, Art Unit 1648